REMARKS

1. Preliminary Matters

a. Status of the Claims

Claims 18-29 are pending and under active consideration. Claim 18 is amended. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of this application. Upon entry of the amendments, claims 18-29 will be pending and under active consideration.

b. Amendments to the Claims

Claim 18 is amended to remove the limitation "a sequence at least 80% identical to (a) or (b)," without prejudice to seeking broader claims in a continuing application.

2. Patentability Remarks

a. 35 U.S.C. § 102

On pages 3 and 4 of the Office Action, the Examiner rejects claims 18 and 24 under 35 U.S.C. § 102(b) as allegedly being anticipated by Hood *et al.* (U.S. Pat. Pub. No. 2002/0150891) ("Hood"). The Examiner asserts that Hood teaches a nucleic acid with SEQ ID NO: 470 that is at least 80% identical to 16 or more consecutive nucleotides of instant SEQ ID NO: 2240728 and to a vector comprising the nucleic acid. However, amended claim 18 does not recite the limitation "a sequence at least 80% identical to [at least 16 consecutive nucleotides of SEQ ID NO: 2240728]." Applicant submits that Hood does not teach or suggest a nucleic acid with a sequence that is identical to at least 16 consecutive nucleotides of SEQ ID NO: 2240728, nor does Hood teach or suggest a vector comprising this nucleic acid. Accordingly, Hood does not anticipate the subject matter of claims 18 or 24. In view of the foregoing amendment and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 18 and 24 under 35 U.S.C. § 102.

b. 35 U.S.C. § 101

On pages 4-6 of the Office Action, the Examiner rejects claims 18-29 under 35 U.S.C. § 101 because the claimed invention allegedly lacks support from either a specific and substantial asserted utility or a well established utility. In order to satisfy the utility requirement, a specific and substantial utility must either (i) be cited in the specification or (ii) be recognized as well as established in the art, and the utility must be credible. *See In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005) and *Revised Interim Utility Guideline Training Materials* ("*Guidelines*").

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See Fisher* 421 F.3d at

1371 and *Guidelines*. Applicant respectfully submits that the application provides a specific utility for the claimed microRNA-related nucleic acids in accordance with *Fisher* and *Guidelines*.

In *Fisher*, the claims at issue were directed to five (5) out of more than 32,000 EST that were disclosed in the application. Each of disclosed ESTs were from a cDNA library of pooled leaf tissue isolated from a maize plant. The *Fisher* application did not disclose the location of the ESTs in the genome or the function of the underlying genes. *Fisher* asserted that the utilities for claimed ESTs were (1) serving as a molecular marker; (2) measuring the level of mRNA in a tissue sample; (3) provide a source of primers for PCR of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *See Fisher*, 421 F.3d at 1367-1368. It is important to note that each of the utilities asserted were not limited to any specific gene, genetic location or protein.

The *Fisher* court concluded that the asserted utilities were clearly not "specific." The court explained that any EST transcribed from any gene in maize could perform the seven uses such as being a molecular marker, a primer, or measure the level of RNA in a tissue sample. In other words, nothing about the seven alleged uses separated the claimed ESTs from the vast number of other ESTs also disclosed in the application. The keystone to the lack of specific utility in *Fisher* is that the claimed ESTs **did not correlate to an underlying gene of known function found in the maize genome**.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids may be used to target and modulate expression of **specific** gene transcripts. Table 7, lines 1900809-1900813 and Table 8, lines 4903950-4903970 of the application disclose that the claimed microRNA-related sequences specifically target mRNA transcripts of the SRY gene. Consequently, the claimed nucleic acids are of a **specific and unique nature** because these nucleic acids regulate the translation of mRNAs from the **specific target gene SRY**. Accordingly, the asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating SRY.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public. *See Id.* at 1371 and *Guidelines*. Applicant respectfully submits that the application provides a substantial utility for the claimed microRNA-related nucleic acids in accordance with *Fisher* and *Guidelines*.

In *Fisher*, it was admitted that the underlying genes for the ESTs had no known function. *Fisher* argued that this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, *Fisher* failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that

the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Fisher*, 421 F.3d at 1373, quoting *Brenner v. Manson*, 383 U.S. 519 (1966).

In further sharp contrast to *Fisher*, the present application discloses that the claimed nucleic acids may be used to bind and regulate mRNA transcripts of the SRY gene. *Instant Application*, Table 8, lines 4903950-4903970. At the time of filing, it was known that SRY is a mammalian sex-determining gene that encodes a HMG domain-containing protein. *See* Harley VR *et al.* Endocrine Reviews 2003;24(4):466-487 ("Harley"). It was further known that absence of SRY leads to gonadal dysgenesis in males. *Id.* It was additionally known that a transgene capable of expressing SRY is sufficient to transform mice that have XX sex chromosomes (*i.e.*, are female) to develop as males. *See* Wagner CK *et al.* Endocrinology 2004;145(3):1046-9 ("Wagner"). Moreover, SRY was known to be sufficient to induce gonadal hormone levels normal levels in male mice lacking a functional Y chromosome. Accordingly, SRY expression could be modulated to alter the level of an SRY transgene, and thereby affect gonadal hormone levels and male development.

The evidence described above clearly supports that the claimed nucleic acids have a number of presently available benefits to the public. Such benefits are the ability to modulate the expression of SRY in order to affect gonadal hormone levels and male development. In view of the application providing particular targets of known function for the claimed microRNA-related nucleic acids, Applicant respectfully submits that the specific and substantial utility requirements are satisfied in accordance of *Fisher* and *Guidelines*.

(3) Credible Utility

An asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided. An assertion is credible unless (i) the logic underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Accordingly, the invention must be operable to achieve useful results. *See Guidelines* at page 5 and *In re Swartz*, 232 F.3d 862 (Fed. Cir. 2000). The proper inquiry for determining credible utility is whether a person of ordinary skill in the art would conclude that the asserted utility is more likely true than not. Applicant respectfully submits that the record clearly shows that one of ordinary skill in the art would believe that the claimed nucleic acids may be used to modulate expression of the specific mRNA targets.

Dr. Yitzhak Pilpel, who is an expert in the field of microRNA and RNAi biology, states in the attached declaration (Appendix) that the claimed nucleic acids would likely inhibit expression of SRY mRNA transcripts. Dr. Pilpel's opinion is based on a number of facts.

(a) Characteristics of microRNA-target mRNA binding

Dr. Pilpel states that researchers in the microRNA field believed that there are a number of characteristics of inhibition of protein expression via target mRNA interference by an endogenous or synthetic nucleic acid of 18-25 nucleotides in length, such as a microRNA. For example, the 5' end of the microRNA may contain a "seed" that is full complementary between the first 1-8 base pairs of the 5' of the microRNA and the target mRNA. *See* ¶¶ 2 and 3, Pilpel Declaration. This seed may be conserved and is often flanked by adenosine. *See* ¶ 3, Pilpel Declaration. If there is insufficient base-pairing of the microRNA 5' seed there may be compensatory complementation at the 3' end of a microRNA and its target mRNA sequence. *See* ¶ 3, Pilpel Declaration. Finally, although not obligatory, there may be multiple binding sites for a microRNA on a mRNA target, which may enhance the binding effect of target repression. *See* ¶ 3, Pilpel Declaration.

Importantly, Dr. Pilpel states that the claimed nucleic acid sequence as set forth in SEQ ID NO: 8385 and its respective target gene sequences of SRY (as depicted in column B, row 2, p. 4, Table A) are consistent with the characteristics of the microRNA:target mRNA binding described above. *See* ¶ 6, Pilpel Declaration. In view of these conserved characteristics, Dr. Pilpel concludes that the microRNA of SEQ ID NO: 8385 (column B, row 2, p. 4, Table A) is likely to inhibit expression of the protein encoded by the target gene SRY in view of the characteristics of microRNA:mRNA binding properties. *See* ¶ 6, Pilpel Declaration.

(b) MicroRNA algorithms

Dr. Pilpel states several effective microRNA:target algorithms have been based upon the characteristics of microRNA:target mRNA binding described above. *See* ¶ 4, Pilpel Declaration. Dr. Pilpel provides TargetScan (developed by Lewis *et al., Cell* 115:787-798 (2003)) and miRanda (developed by Enright *et al.*, *Genome Biology* 5:R1 (2003)) as examples of such algorithms. The TargetScan algorithm predicted 15 targets of various miRNAs identified by Lewis, and 11 of the predicted interactions between a particular miRNA and target mRNA were biologically validated with a false positive rate between 22 and 31%. The miRanda algorithm was also an effective microRNA:target algorithm, where 9 out of 10 predicted targets identified by the miRanda algorithm in Enright were biologically validated with a 24-39% false positive rate. *See* ¶ 4, Pilpel Declaration. MicroRNA:target interactions were also further validated by virtue of target binding site conservation among multiple organisms. *See* ¶ 5, Pilpel Declaration.

Importantly Dr. Pilpel states that SEQ ID NO: 8385 and its respective target gene sequences of SRY are consistent with microRNA and target mRNAs predicted by the algorithms described above. *See* ¶¶ 4 and 5, Pilpel Declaration. In view of these facts, Dr. Pilpel concludes that the microRNA of SEQ ID NO: 8385 is likely to inhibit expression of the protein where co-expressed. See ¶ 6, Pilpel Declaration.

(c) SRY

Applicant further submits that SRY is a credible target for trans-acting regulatory elements. Specifically, the Pilpel Declaration indicates that the claimed nucleic acids are capable of binding SRY with 12 out of 22 nucleotides of complementarity, as demonstrated at Table 7, lines 1900809-1900813 of the specification, and as shown below.

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                    --  - -- CCCT-
SRY                 5'   AC A  G     CACTTTCT 3'
SEQ ID NO: 8385     3'   TG T  C     GTGAAAGA 5'
                       AG  G TT CCTTC
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In view of the foregoing, Applicant asserts that a person of ordinary skill in the art would more than likely conclude that the claimed nucleic acids may be used to modulate expression of the SRY transcript, which in turn may respectively alter gonadal hormone levels and male development. Accordingly, a proper credible utility is asserted for the claimed nucleic acids. Applicant respectfully asserts that a specific and substantial utility has been demonstrated both in the specification and by what was recognized as well as established in the art at the time of filing, and the utility is credible. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 101.

c. 35 U.S.C. § 112, first paragraph

(1) In view of alleged lack of utility

On page 6 of the Office Action, the Examiner rejects claims 18-29 under 35 U.S.C. § 112, first paragraph, because the claimed invention allegedly is not supported by either a specific and substantial asserted utility or a well established utility. Applicant respectfully disagrees. In view of the claimed subject matter having credible, specific, and substantial utility as described above, Applicant submits that the specification enables the claimed subject matter and respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

(2) 80% identity to a portion of SEQ ID NO: 2240728

On pages 6 and 7 of the Office Action, the Examiner rejects claims 18-29 under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement. The Examiner asserts that nucleic acid molecules with as little as 80% identity to a portion of SEQ ID NO: 2240728 have not been adequately described in the specification. Amended claim 18 no longer recites sequences with as little as 80% identity to at least 16 consecutive nucleotides of SEQ ID NO: 2240728. Consequently, the claimed nucleic acids are 100% identical to at least 16 consecutive nucleotides of SEQ ID NO: 2240728. Applicant submits that one of skill would readily conclude that Applicant was in possession of the claimed nucleic acids. In view of the foregoing amendment and remarks, Applicant

respectfully requests that the Examiner reconsider and withdraw the rejection of claims 18-29 under 35 U.S.C. § 112, first paragraph.

(3) Alleged lack of enablement

On page 7 of the Office Action, the Examiner rejects claims 18-29 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. The Examiner asserts that there is no support in the instant specification for the claimed nucleic acids functioning as miRNAs, and that the claimed nucleic acids lack utility. Applicant respectfully disagrees. As described above, the claimed nucleic acids have a credible, specific and substantial utility, namely in modulating expression of the SRY transcript, which in turn may respectively alter gonadal hormone levels and male development. Moreover, Table 7, lines 1900809-1900813 and Table 8, lines 4903950-4903970 of the application as filed disclose this asserted utility of the claimed nucleic acids to inhibit SRY. Therefore, Applicant submits that the function of the claimed nucleic acids was known at the time of filing. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 18-29 under 35 U.S.C. § 112, first paragraph.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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Dated: May 27, 2008

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